Treatment and prevention of pain due to vaso-occlusive crises in adults with sickle cell disease: an educational void

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Pain due to vaso-occlusive crisis is the major cause of hospital use in sickle cell disease. Although available guidelines provide recommendations for opioid administration in this setting, only 4 (21%) of 19 medical textbooks present treatment regimens that are consistent with them. Moreover, only 7 texts (37%) note that addiction is infrequent in this population, while 11 (92%) of 12 texts provide such reassurance for cancer-related pain ($P < .005$). Finally, hydroxyurea use to decrease the frequency of vaso-occlusive crises is completely defined only in 2 textbooks. Thus, most medical texts provide neither adequate information for the treatment or prevention of pain due to vaso-occlusive crisis in sickle cell disease nor reassurance of the unlikelihood of addiction in this population. In contrast, treatment recommendations for less common hematologic disorders are consistent with current standards in 53% to 84% of appropriate texts ($P < .05$). Limited knowledge regarding the principles and appropriateness of opioid therapy; a lack of evidence-based research on pain control; and misconceptions and prejudices about drug abuse and addiction contribute to this educational void. Thus, research and training on pain control in sickle cell disease are needed to parallel studies of environmental and genetic factors contributing to the known clinical heterogeneity of this disorder. (Blood. 2008;111:997-1003)

Introduction

Sickle cell disease (SCD) affects approximately 72 000 individuals in the United States. Subjects with these disorders may suffer frequent vaso-occlusive crises (VOCs) marked by severe pain often requiring parenteral opioid administration in hospital emergency departments and inpatient units.[1] Guidelines for the management of pain due to VOCs in SCD, published in both the United States[2] and Great Britain,[3] have been available since 1999 and 2003, respectively. In the United States, these guidelines are also incorporated into a document on the management of SCD published by the National Institutes of Health (NIH) in 2002.[4] However, patients and their families frequently express dissatisfaction with the care they receive in acute care settings.[5] Moreover, while treatment with hydroxyurea was shown to decrease the incidence of VOCs in 1995, this medication is still underused.[6-8] These observations prompted a review of 19 textbooks in hematology, internal medicine, and emergency medicine published during or after the year 2003 to identify barriers to the effective management of VOCs in SCD.[9-27] (Specific chapters reviewed in each textbook are listed in Document S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Guideline recommendations for opioid use for VOCs in SCD

The 4 essential features of both guidelines are (1) rapid initiation of opioid therapy (within 15-30 minutes of arrival in the emergency department); (2) use of an adequate opioid starting dose; (3) frequent repeat doses of opioids (every 15-30 minutes) until pain is significantly improved; and (4) the need to select treatment regimens based on an individual's prior opioid-response history (Table 1).[2-4] The guidelines differ somewhat in their recommendations for the doses of opioid to be used when knowledge of prior opioid requirements is limited. Thus, the American Pain Society (APS) suggests an initial loading dose of morphine of 5 to 10 mg (or 1.5 mg hydromorphone) in adults weighing at least 50 kg with repeat doses being one quarter to one half of the loading dose given every 15 to 30 minutes with increasing dose titration to pain relief.[2,4] In contrast, the British Committee for Standards in Hematology (BCSH) suggests a loading dose of 0.1 mg/kg morphine with the same dose repeated every 20 minutes until effective analgesia is achieved.[3] Both guidelines also indicate the need to monitor patients carefully for respiratory depression and other adverse effects of opioid therapy.

Physician knowledge of guideline practices

Unfortunately, most physicians are not familiar with these guidelines or with the treatment approaches they suggest. In an informal survey at our institution, none of 7 attending physicians on the adult hematology service (myself included) and none of 5 attending physicians in the emergency medicine department had any awareness of the existence of either guideline. Moreover, lack of awareness of guidelines may translate into inadequate patient care. Thus, in 2004, only 46% of 79 medical directors of American pain clinics indicated that opioids had a major role in the treatment of pain related to sickle cell disease, while 6% indicated that opioids were a last resort and 4% felt that opioids had no role whatsoever.[28] Similarly, in 2005, 25% of 109 physicians surveyed at 7 institutions with NIH-funded university-based comprehensive sickle cell centers indicated that a morphine dose of 2 mg

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Table 1. Opioid use in the treatment of pain in adult patients with VOC due to SCD

Text	Time to first dose	Parenteral opioid		Need to individualize	Refer to guidelines
		Dose	Frequency		
Guidelines					
APS[2]/NIH[4]	15-20 min	5-10 mg morphine *or* 1.5 mg hydromorphone	15-30 min*	Yes	N/A
BCSH[3]	<30 min	0.1 mg/kg morphine	<20 min†	Yes	N/A
Hematology					
Wintrobe's[9]	Not stated	Not stated	Not stated	Not stated	No
Hoffman[10]	"Prompt"	Morphine 0.1-0.15 mg/kg	20 min	Not stated	Yes
Williams[11]	Not stated	Not stated	Not stated	Not stated	Yes
Handin et al[12]	Not stated	Not stated	Not stated	Yes	No
Bethesda[13]	Not stated	Not stated	Not stated	Yes	Yes (NIH)
Boyiadzis et al[14]	Not stated	5-10 mg morphine *or* 1.5 mg hydromorphone	2-4 h‡	No§	Yes (both)
Young et al[15]	"Rapid"	5-10 mg morphine	30 min‖	Yes	Yes (NIH)
Hillman et al[16]	Not stated	Not stated	Not stated	Not stated	No
Hoffbrand et al[17]	Not stated	Not stated	Not stated	Yes	No
Emergency medicine					
Rosen's[18]	Not stated	Morphine 0.15 mg/kg (up to 10 mg)¶	Not stated	Not stated	No
Tintinalli[19]	Not stated	Not stated	Not stated	Yes	No
Harwood-Nuss'[20]	Not stated	Not stated	Not stated	Yes	No
Internal medicine					
Oxford[21]	Not stated	Morphine 0.1 mg/kg#	1 h	Not stated	No
Cecil[22]	Not stated	Morphine 0.1 mg/kg (up to 10 mg) *or* hydromorphone 0.01-0.02 mg/kg	3-4 h	Not stated	No
Washington Manual[23]	Not stated	Morphine 0.1-0.2 mg/kg *or* hydromorphone 0.02-0.04 mg/kg**	2-3 h**	Yes	Yes
ACP Medicine[24]	"Rapid evaluation"	Morphine 10 mg *or* hydromorphone 4 mg	30 min ×1††	Not stated	No
Harrison's[25]	Not stated	Morphine 0.1-0.15 mg/kg	3-4 h	Not stated	No
Conn's[26]	Not stated	Hydromorphone 2-4 mg‡‡	30-45 min‡‡	Not stated	No
Up-to-date[27]	Not stated	Morphine 2 mg infused over 4-5 min§§	1-3 h§§	Not stated	Yes

Doses are given for intravenous or subcutaneous administration.
APS indicates American Pain Society; NIH, National Institutes of Health; N/A, not applicable; and BCSH, British Committee on Standardization in Haematology.
*Use 1/4 to 1/2 of initial dose for follow-up treatment.
†Use the same dose as the initial dose for follow-up treatment.
‡Patient is assessed every 15 to 30 minutes but opioid doses indicated as every 2 to 4 hours.
§Individualization suggested only for patients on chronic opioid therapy.
‖Use 2.5 to 5.0 mg morphine every 30 minutes until pain relieved.
¶Or morphine 5 mg bolus then 5 mg/h by PCA.
#Or morphine infusion at 2 mg/min (maximum=10 mg) but further doses not specified, or diamorphone 0.05 mg/kg subcutaneously or intramuscularly.
**Or morphine by PCA infusion at 2 mg/h plus 2- to 10-mg boluses every 6 to 10 minutes.
††See "Textbook recommendations for opioid use for VOCs in SCD."
‡‡Recommended for opioid-naive patients. For others, 4 to 8 mg hydromorphone can be infused over 15 to 20 minutes with a 4-mg dose repeated in 30 minutes.
§§Chapter on SCD refers to chapter on "Pain Control in the Intensive Care Unit" where these recommendations were obtained. Can increase morphine dose by 1 to 2 mg every 1 to 3 hours.

intravenously every 4 to 6 hours was appropriate or excessive treatment for pain in a 66-kg man with SCD, while 33% thought that a morphine dose of 10 mg intravenously every 3 hours was either overtreatment or inappropriate.[29]

Textbook recommendations for opioid use for VOCs in SCD

The reason for this lack of knowledge is apparent from a review of the standard medical textbooks. As shown in Table 1, none of the reference works indicate a target time for the initiation of opioid therapy, and only 7 texts (37%) comment on the need to individualize therapy based on patient history. Suggested starting doses of morphine or hydromorphone are not given in 8 (42%) of the 19 references reviewed including 6 of the 9 hematology texts and 2 of the 3 emergency medicine texts. In the 11 other reference works, suggested starting opioid doses are consistent with or higher than guideline recommendations in 10 and lower than guideline recommendations in one.

The initial frequency of opioid administration is not suggested in 9 (47%) of these 19 references, only 3 of the 10 remaining texts suggest repeat opioid doses within a 20- to 30-minute interval, and 1 text suggests an interval of 30 to 45 minutes. Moreover, while one text notes that one half of the initial dose can be given 30 minutes after the first dose if pain is not adequately controlled, it is not clear whether additional doses can be given at 30-minute intervals for persistent poor pain control prior to resuming full-dose therapy every 2 hours.[24] Thus, overall, the frequency of opioid administration suggested is consistent with guidelines in 4 texts (21%) but only if this ambiguity is ignored and if the somewhat more extended interval of 30 to 45 minutes is accepted.[26]

Only 7 texts cite either guideline in their lists of references.[10,11,13-15,23,27] Nonetheless, treatment recommendations are consistent with these guidelines in only 2 of them.[10,15]

Comparison with opioid use in other acute pain settings

VOC is often treated by physicians with little experience in acute pain management in other settings. Thus, the analgesic regimens

Table 2. Comparison of acute pain treatment guidelines

Clinical setting	Reference	Protocol for intravenous morphine	Maximum morphine in first hour of treatment, mg*
VOC in SCD	APS[2]/NIH[4]	5-10 mg then 2.5-5.0 mg every 15-30 min†	10-30
	BCSH[3]	0.1 mg/kg every 20 min	21‡
Acute coronary syndromes	ACC/AHA[30]	2-4 mg every 5 min	25-30§
Postoperative pain	YNHH PACU	2-5 mg every 3-5 min‖	20-60
Emergency department acute pain treatment	Harwood-Nuss'[20]	2-5 mg every 5 min	24-60

YNHH indicates Yale New Haven Hospital; and PACU, postanesthesia care unit.

*As intravenous morphine equivalents.

†See Table 1.

‡Based on patient weight of 70 kg.

§Reference notes that 25 to 30 mg may be required.

‖Unpublished protocol calls for 2 mg morphine intravenously every 3 to 5 minutes if pain is moderate (maximum = 10-20 mg) or 5 mg morphine intravenously every 3 to 5 minutes if pain is severe (maximum = 60 mg).

suggested in the current guidelines may seem to require particularly high opioid doses administered at unusually frequent intervals. However, as shown in Table 2, while protocols used in different acute pain settings vary somewhat, maximum opioid administration allowed for in the first hour of treatment of patients with VOC is actually the same or less than that proscribed for the acute coronary syndromes, postoperative pain management, and the general treatment of acute pain in the emergency department.

Surprisingly little has been published about the actual opioid doses administered to adults with VOC. Gonzalez et al, using a protocol similar to the APS guideline, reported that 41.0 plus or minus 17.6 mg morphine was administered intravenously during emergency department visits by 12 adult sickle cell patients over a time frame of 5.5 plus or minus 1.6 hours.[31] In our recent experience, there was a more than 10-fold interindividual variation in the total opioid requirement during the first 24 hours of admission of patients with VOC who were not on long-acting opioids (Table 3). Nonetheless, the mean opioid requirement in these patients was similar to that used postoperatively in representative studies after liver resection, caesarian section, total abdominal hysterectomy, knee surgery, and spinal surgery (Table 3).[32-36] This is particularly noteworthy since increased opioid metabolism has been demonstrated in the setting of SCD both in humans and in transgenic mice.[37,38] Although these comparisons are limited by the lack of uniform pain control end points and adjustment for patient weight, they provide a framework that suggests that opioid requirements in SCD are indeed proportional to those in other severe acute pain settings. Importantly, patients on chronic long-acting opioid therapy are likely to require higher opioid doses for the treatment of acute pain because of the development of tolerance and the occurrence of hyperalgesia.[4,39]

Concerns about opioid addiction and drug abuse

It is well recognized that objective measures of the presence and severity of pain are lacking. Moreover, studies of patients with advanced malignancy suggest that clinical caregivers frequently underestimate the severity of pain.[40] This has led to the core concept of pain treatment: "believe the patient!" Nonetheless, 86% of physicians in university hospital settings do not believe that self-report is the most reliable indicator of the existence and intensity of pain in patients with SCD.[29]

Weighed against this concept is the pervasive and unfounded fear of drug addiction and drug-seeking behavior in acute and chronic pain patients in general and the SCD population in particular.[41-43] For example, 26% of hematologists and 53% of ED physicians in one survey believed that at least 20% of SCD patients are addicted.[42] Moreover, health care personnel consistently indicated that SCD patients were almost twice as likely to be opioid dependent as other pain patients presenting to an emergency department.[41] In fact, however, estimates of the incidence of this problem in SCD patients parallel those in the community at-large (Table 4).[44-48] Thus, 8 (8.3%) of 96 patients older than 18 years in the adult SCD program at Yale New Haven Hospital have exhibited behaviors consistent with substance abuse. This incidence is similar to that reported in the population as a whole in New Haven in 1984 and in Connecticut in 2004 to 2005.[47,48] Moreover, many behaviors construed as indicative of addiction in SCD patients often result from undertreatment of pain (ie, pseudoaddiction).[50] Finally, racial prejudices also contribute to ineffective pain

Table 3. Comparison of actual opioid use in adults in different acute pain settings

Clinical setting	Reference	N	Opioid use in first 24 hours
VOC in SCD	Solomon*	24	64.7 ± 41.0 (16-157)
Postoperative			
Liver resection	Roy et al[32]	10	87 ± 34
Spinal surgery	Jarvey et al[33]	20	51.1 ± 20.8
Total abdominal hysterectomy	Gan et al[34]	20	59.1 ± 27.4†
C-section	Bell et al[35]	28	67 ± 28
Knee surgery	Loper and Ready[36]	17	64 ± 24 (32-101)

Opioid use values are given as means plus or minus 1 standard deviation for intravenous morphine equivalents except where noted, and numbers in parentheses are ranges of doses administered.

VOC indicates vaso-occlusive crisis; SCD, sickle cell disease; and C-section, caesarian section.

*Unpublished observations for 24 consecutive in-patient hospital admissions in 21 adult SCD patients from March 1, 2006, through February 28, 2007, who were not on chronic long-acting opioids.

†Value is mean plus or minus 1 SEM.

Table 4. Comparison of addiction and substance abuse in adults with sickle cell disease and those in the community at-large

Population/ location	Year	Age, y	Addiction or substance abuse, no./no. (%)
Adult SCD patients			
Cincinnati[44]	1989	Not stated	14/160 (9)
Philadelphia[45]	1992	Not stated	0/50† (0)
London[46]	2002	Not stated	4/800 (0.5)
New Haven*	2007	All	8/96 (8.3)
		18-25	2/31 (6.5)
Community at-large			
St Louis[47]	1981-82	Lifelong	6.4 ± 1.0%‡
Baltimore[47]	1981-82	Lifelong	7.3 ± 0.9%‡
New Haven[47]	1980-81	Lifelong	6.4 ± 1.3%‡
Connecticut[48]	2004-05	18-25	8.83% (6.90-11.23)§

SCD indicates sickle cell disease.
*Solomon, unpublished observations, June 2007, based on criteria of Savage.[49]
†All patients were on long-acting opioids for 2 years.
‡Values are means ± SEM for African-Americans as %.
§Numbers in parentheses are 95% prediction interval as %.

management in this population.[51] These misconceptions and prejudices can lead to clinician behaviors that seriously compromise patient care.[52]

It is unfortunate then that only 7 (37%) of the 19 texts reviewed provide reassurance of a low risk of opioid addiction in sickle cell patients (Table 5). In contrast, sections on pain treatment in advanced cancer were present in 12 texts, and reassurance of the low risk of opioid addiction in this setting is provided in 11 of them (91%) ($\chi^2 = 8.941$; $P < .005$). Similar reassurance is also provided in the chapters on acute pain management in all 3 emergency medicine texts.[18-20]

Textbook recommendations for hydroxyurea use in the treatment of SCD

The Multicenter Study of Hydroxyurea (MSH) published in 1995 treated patients with at least 3 severe VOCs/year with hydroxyurea at an initial dose of 15 mg/kg per day.[6] This dose was increased by 5 mg/kg per day every 12 weeks up to a maximum of 35 mg/kg per day as long as the neutrophil count exceeded 2×10^9/L. As shown in Table 6, only 8 (50%) of the 16 hematology and internal medicine texts provided a reasonable indication for hydroxyurea therapy and this was vague in 6 of them; only 8 texts (50%) gave an initial dose of hydroxyurea consistent with the published studies; only 4 texts (25%) provided an appropriate schedule for increasing the dose of hydroxyurea; and only 5 texts (31%) noted the need to maintain the neutrophil count higher than 2×10^9/L. Moreover, only 2 texts (13%) met all 4 of the criteria listed. (Emergency medicine texts were excluded from this analysis.)

Textbook recommendations for the treatment of other hematologic disorders

Treatment recommendations for von Willebrand disease (VWD), hemophilia A, β-thalassemia major (β-Thal), thrombotic thromobocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP), and acute myelogenous leukemia (AML) were also reviewed. Textbook recommendations were considered consistent with current standards of practice if they met *all* of the recommendations for each disorder (Table S1). As shown in Table 7, with the exception of VWD, these disorders have incidence rates or prevalence rates significantly lower than that of SCD. Nonetheless, treatment recommendations consistent with generally accepted standards of care are given in 53% to 84% of texts. Overall, textbooks were significantly less likely to meet guidelines for both opioid and hydroxyurea therapy in SCD than treatment standards in all the other hematologic disorders reviewed ($\chi^2 > 4.07$; $P < .05$).

Table 5. Risk of addiction and opioid therapy in SCD and cancer

Text	Cancer-related pain	Pain due to VOC in SCD
Hematology		
Wintrobe's[9]	Reassurance	Reassurance
Hoffman[10]	Reassurance	Reassurance
Williams[11]	Reassurance	Reassurance
Handin et al[12]	Not applicable*	Reassurance
Bethesda[13]	Not applicable*	Not addressed
Boyiadzis et al[14]	Reassurance	Not addressed
Young et al[15]	Not applicable*	Not addressed
Hillman et al[16]	Not applicable*	Reassurance
Hoffbrand et al[17]	Not applicable*	Not addressed
Emergency medicine		
Rosen's[18]	Reassurance	No reassurance given
Tintinalli[19]	Not applicable*	Not addressed
Harwood-Nuss'[20]	Not applicable*	Reassurance
Internal medicine		
Oxford[21]	Reassurance	Not addressed
Cecil[22]	Not addressed	Not addressed
Washington Manual[23]	Reassurance	Not addressed
ACP Medicine[24]	Reassurance	No reassurance given
Harrison's[25]	Reassurance	Not addressed
Conn's[26]	Reassurance	Reassurance
Up-to-date[27]	Reassurance	Not addressed

VOC indicates vaso-occlusive crisis; and SCD, sickle cell disease.
*Not applicable indicates that text did not have a section on cancer-related pain.

Electronic media and medical literature as educational resources

Since many (albeit not all) physicians involved in the care of adults with SCD have access to online electronic medical journal publications (usually in university settings), these resources were also reviewed. Searches were performed using "the disease name + therapy/therapeutics" as keyword search terms with Medline/PubMed, which is universally available on the National Medical Library website (http://www.nlm.nih.gov).[53] This consistently resulted in more than 1200 "hits" for each disorder. Therefore, to make these searches more usable, references were then limited to review articles involving human subjects that were written in English and that appeared in core medical journals during the last 10 years. Pediatric journals were excluded except for the treatment of thalassemia and hemophilia A. The findings paralleled those in the medical textbooks. Thus, as shown in Table 8, none of the 4 review articles identified provided adequate information on opioid use in VOC and only 1 of 9 review articles provided sufficient information on hydroxyurea therapy. Moreover, the BCSH guideline paper was not identified by this search strategy.[3] In contrast, reviews meeting the treatment criteria in Table S1 were easily identified for all other hematologic disorders evaluated with the exception of hemophilia.

Table 6. Textbook recommendations for hydroxyurea therapy in SCD

Text	Indications	Initial dose, mg/kg per day	Dose increments, amount/frequency	Monitoring
MSH, 1995[6]	≥3 severe VOCs/y	15	5 mg/kg per day every 12 wk	ANC >2×10^9/L
NIH, 2002[4]	Frequent severe VOCs*	10-15	Increase every 6-8 wk (increment not stated)	ANC >2.5×10^9/L*
Hematology				
Wintrobe's[9]	Frequent VOCs	Not stated	Not stated	Not stated
Hoffman[10]	"Treatment of pain crises"	0.15	0.3 mg/kg per day (frequency not stated)	ANC >2×10^9/L
Williams[11]	Not stated	15	5 mg/kg per day every 12 wk	WBC >2×10^9/L†
Handin et al[12]	Frequent pain‡	15	5 mg/kg per day every 8 wk	ANC >2×10^9/L
Bethesda[13]	Frequent pain	10-15	5 mg/kg per day every 6-8 wk	ANC >2×10^9/L§
Boyiadzis et al[14]	Not stated	10-15	5 mg/kg per day every 12 wk	ANC >2.5×10^9/L
Young et al[15]	Frequent pain‖	Not stated	Not stated	Not stated
Hillman et al[16]	Not stated	10-15 or 500 mg/d	Increase to 1.0 g/d at 6-8 wk	Not stated
Hoffbrand et al[17]	Frequent pain‡	15	Up to 25 mg/kg per day	Not stated
Internal medicine				Not stated
Oxford[21]	Not stated	Not stated	Not stated	Not stated
Cecil[22]	Impaired by VOC	15	Increase to maximum tolerated	Not stated
Washington Manual[23]	Not stated	15-35 #	Not stated	Not stated
ACP Medicine[24]	Not stated	15	Not stated	Not stated
Harrison's[25]	≥3 VOCs/y**	10-30#	Not stated	WBC = 5-8×10^9/L
Conn's[26]	≥3 VOCs/y	Not stated	Not stated	Not stated
Up-To-Date[27]	Not stated	Not stated	Not stated	Not stated

MSH indicates multicenter study of hydroxyurea, NIH, National Institutes of Health; VOC, vaso-occlusive crisis; ANC, absolute neutrophil count; and WBC, white blood cell count.

*Other indications include acute chest syndrome, other severe vaso-occlusive events and severe anemia. Additional monitoring criteria include platelet count higher than 95×10^9/L.

†Additional monitoring criteria include hemoglobin level more than 45 g/L (4.5 g/dL) and reticulocyte count higher than 80×10^9/L.

‡Another indication is the acute chest syndrome.

§Additional monitoring criteria include reticulocyte count higher than 100×10^9/L and platelet count higher than 90×10^9/L.

‖Another indication is recurrent acute chest syndrome.

#Only a dose range given in Washington Manual and Harrison's without details on initial dose or dose adjustment.

**Severe VOC is defined as requiring hospitalization and recurrent acute chest syndrome is given as another indication for hydroxyurea treatment.

Are the guidelines effective?

Although randomized controlled trials have not been conducted, use of guideline recommendations appears to improve the quality of care of patients with VOC by shortening the time to pain relief and decreasing the need for hospitalization when used in both specialized day hospital units and emergency room settings.[54-56] In fact, even more intensive regimens may be warranted. Thus, a dose of 0.1 mg/kg morphine intravenously has recently been shown to have only limited effectiveness at 30 minutes in treating acute pain in the emergency room.[57]

Where to look

Although not easily accessible, comprehensive discussions of pain in SCD and its management have been written by both Ballas[58] and Benjamin.[59] Much of the information in the former monograph can be found in guideline form through the City of Hope Pain and Palliative Care website (http://www.cityofhope.org/prc/). The 2002 NIH monograph on the management of sickle cell disease[4] can also be obtained at both the City of Hope website and the Sickle Cell Center Information website of the Georgia Comprehensive Sickle Cell Center at Grady Health System (http://www.scinfo.org).

Table 7. Treatment recommendations for hematologic disorders in medical textbooks

Hematologic disorder	Estimated US prevalence or incidence*	Adequate treatment recommendations†, no./no. (%)			
		Hematology texts	Emergency medicine texts	Internal medicine texts	All texts
SCD, opioid therapy	72 000	2/9† (22)	0/3 (0)	2/7‡ (29)	4/19‡ (21)
SCD, hydroxyurea therapy	72 000	2/9 (22)	0/3 (0)	0/7 (0)	2/19 (11)
VWD	3 000 000	9/9 (100)	1/3 (33)	5/7 (71)	15/19 (79)
Hemophilia A	17 000	7/9 (78)	3/3(100)	6/7 (86)	16/19 (84)
β-Thal	1 000	7/9 (78)	0/3 (0)	5/7 (71)	12/19 (63)
TTP	1 100	5/9 (56)	1/3 (33)	4/7 (57)	10/19 (53)
ITP	15 000	8/9 (89)	1/3 (33)	6/7 (86)	15/19 (79)
AML	11 000	9/9 (100)	0/3 (0)	4/7 (57)	13/19 (68)

SCD indicates sickle cell disease; VWD, von Willebrand disease; β-Thal, β-thalassemia major; TTP, thrombotic thrombocytopenic purpura; ITP, immune (or idiopathic) thrombocytopenic purpura; and AML, acute myeloid leukemia.

*Prevalence rates are given for SCD, VWD, hemophilia A, and β-Thal, and incidence rates are given for TTP, ITP, and AML. Units are number of cases in country.

†See Table S1 for criteria used.

‡Based on recommendations given in text for Hoffman et al[10] and single breakthrough dose at 30 minutes given in ACP Medicine.[24] If recommendations given in table in Hoffman et al and requirement for continued therapy at least every 30 minutes are considered, compliance is 1 (11%) of 9 for hematology textbooks; 1 (14%) of 7 for internal medicine textbooks; and 2 (11%) of 19 overall.

Table 8. Treatment recommendations for hematologic disorders review articles in core medical journals 1997 to 2007

Hematologic disorder	Years 1997-1999		Years 2000-2007	
	Relevant reviews, no.*	Met criteria†, no. (%)	Relevant reviews, no.*	Met criteria†, no. (%)
SCD, opioid therapy	N/A‡	N/A‡	4	0 (0)
SCD, hydroxyurea	4	1 (25)	5	0 (0)
VWD	2	2 (100)	2	2 (100)
Hemophilia A	0	0	3	0 (0)
β-Thal	2	1 (50)	2	1 (50)
TTP	1	1 (100)	4	3 (75)
ITP	1	1 (100)	3	3 (100)
AML	2	1 (50)	3	3 (100)

Medline/PubMed searches were performed from the National Library of Medicine website (http://www.nlm.nih.gov) on August 26, 2007, using as keywords the specific hematologic disorder + therapy/therapeutics. Searches were then limited to review articles involving human subjects, written in English, and published in core medical journals during the last 10 years. Pediatric journals were excluded except for the treatment of thalassemia and hemophilia A. See Appendix 2 for specific references.

SCD indicates sickle cell disease; VWD, von Willebrand disease; β-Thal, β-thalassemia major; TTP, thrombotic thrombocytopenic purpura; ITP, immune (or idiopathic) thrombocytopenic purpura; and AML, acute myeloid leukemia.

*Indicates review articles that at least in part addressed treatment of a given disorder.

†See Table S1 for criteria for each disorder.

‡Review articles addressing opioid use for pain control in VOC prior to 2000 were not included since they antedated publication of the first treatment guideline.

Summary and conclusions

Patients with SCD residing in rural areas underutilize services in urban sickle cell centers.[60] Thus, it is important for current guideline recommendations to be readily available to all physicians in family practice, internal medicine, hematology, and emergency room settings. Nonetheless, most standard medical texts provide neither adequate information for the treatment or prevention of pain due to vaso-occlusive crisis in SCD nor reassurance of the unlikelihood of addiction in this population. Nor is this need met by easily obtained review articles in core medical journals. Modern textbooks face a daunting task of incorporating a rapidly expanding body of knowledge into a usable resource that defines the pathogenetic, clinical, and therapeutic aspects of a great many disorders. It is important therefore to review the success with which this goal is met and to direct readers to other readily available resources when space and scope limitations exist. Consideration should also be given to where essential primary source material can be found. While the BCHS recommendations appear in a major hematology journal, this article is not identified by a Medline search for relevant review articles. Moreover, the APS/NIH guidelines exist only as stand-alone publications. Education directed at both increasing awareness of pain treatment guidelines and understanding the behaviors and prejudices of health care professionals that compromise patient care in this setting is greatly needed. Finally, while available guidelines provide frameworks for treatment of VOC in SCD, further research is required to define optimum methods for analgesic intervention in this disorder.[61]

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